Amendments to the Drawings

The attached sheet of drawing includes changes to Figure 4. This sheet, which includes Figure 4, replaces the original sheet including Figure 4. In Figure 4, the panels of Figure 4 have been amended to show panels A, B, and C as described in the specification.

Attachment: Replacement sheet

Remarks

Claims 1-138 are pending. Claims 1, 107, 108, 110, 124, 133, 134, 135, and 136 have been amended to more clearly claim what the applicants consider to be their invention. Claims 137 and 138 have been withdrawn from consideration as being drawn to a non-elected invention.

Claims 1, 107, 108, 110, 124, 133, 134, 135, and 136 were amended to recite decoupling the amplification target circles associated with the analytes from the specific binding molecules. Support for amended claims 1, 68, 78, 85, 87, 89, and 90 can be found at least on page 141, lines 5-6 and page 6, lines 1-4 where method for detecting one or more analytes comprising decoupling amplification target circles associated with the analytes is described. Specifically, the specification provides that amplification target circles not associated with the proteins are removed, the amplification target circles that are associated with the proteins are decoupled from the specific binding molecule and replicated.

Summary of Interviews

Applicant would like to thank the Examiner for her comments during phone calls of October 18, 2006 and October 19, 2006 to discuss the Office Action mailed July 31, 2006 as well as proposed amendments to the claims.

Regarding the proposed amended claims, the Supervisor indicated that the proposed amendments as well as an additional amendment proposed by the Examiner (both of which are represented above in the currently amended claims) would rectify any discrepancies the Examiner had with the claim language as well as assist in overcoming the obviousness rejections.

Objection to the Drawings

The drawings were objected to under 37 CFR 1.83(a) for failing to show (label) the panels for Figure 4 (4A, 4B, and 4C) as described in the specification. Applicants have submitted with this Amendment, a replacement sheet in compliance with 37 CFR 1,121(d), where the panels of Figure 4 have been amended to show panels A, B, and C as described in the specification. Applicants therefore respectfully request withdrawal of this objection.

Rejection Under 35 U.S.C. § 103

A. Claims 1-11, 23-24- 27-65, 70-102, 107-136 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi et al. (U.S. Pat. No. 6,797,474) in view of Abarzua (U.S. Pat. No. 6,498,023). Applicants respectfully traverse this rejection to the extent it applies to the claims as amended.

Applicants first direct the Examiner to the currently amended claims that now recite, in part, "decoupling the amplification target circles associated with the analytes from the specific binding molecules,". These amendments were made in response to the Examiner's comments that such amendments clarified the claims and differentiated the claims over the presently cited art in the 103(a) rejections. Applicants concur and submit that Abarzua et al. does not disclose what is alleged in the Office Action and, as a result, the combination of Lizardi et al. and Abarzua et al. do not disclose or suggest what is presently claimed. In addition, there is no teaching, motivation or suggestion to combine the teachings of Lizardi et al. and Abarzua et al. to achieve the subject matter of the current claims. These errors render the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness.

Applicants submit that, even considered together, Lizardi et al. and Abarzua et al. fail to disclose and suggest every feature of the claimed method. Applicants also submit that statements in the Office Action to the effect that Abarzua et al. teaches decoupling of ATC facilitated by heat denaturation are incorrect. Abarzua et al. included no such disclosure and cannot be interpreted as making such a disclosure, and the Office Action fails to address these points.

In making a determination of obviousness under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that (1) the prior art suggests the invention developed, and (2) the prior art indicates that the invention would have a reasonable likelihood of success. *See In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the applicant has done. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530,

1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The Patent Office has the burden under § 103 to establish a *prima facie* case of obviousness, which can be satisfied only by showing some objective teaching in the prior art would lead one to combine the relevant teachings of the references. *See In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The present rejection does not meet this burden.

Lizardi et al. discloses a method of amplifying and detecting nucleic acid sequences based on the presence of a specific target sequence or analyte (see column 2, lines 58-60). The method employs in part, target-mediated ligation of linear open circle probes (to form circular amplification target molecules) followed by amplification of the amplification target circles by rolling circle amplification (see from column 2, line 63, to column 3, line 44). The Office Action admits that Lizardi et al. does not teach decoupling target circles. (see Office Action page 6, line 6). While Applicant agree that Lizardi et al. fails to teach decoupling target circles, Applicant further submit that Lizardi fails to disclose or suggest digestion, dissociation or separation of amplification target circles associated with an analyte from specific binding molecule associated with an analyte prior to replication of the amplification target circles.

Abarzua et al. discloses a method of synthesizing single-stranded DNA circles of varying size and sequence that are capable of ready use in subsequent processes, such as rolling circle replication (see col. 3, lines 35-47). The method employs the use of hairpin oligonucleotides, each circularized by internal complementary sequences, which are then permitted to anneal to each other via complementary overhangs or coherent tail sequences. After the hairpin oligonucleotides have annealed to one another, the ends of the hairpin oligonucleotides are ligated together to provide a larger single-stranded DNA circle in the form of what Abarzua et al. terms a "dumbbell" (see col. 3, line 67 – col. 4, line 10). Following ligation, the "dumbbell" shaped DNA circle is heat denatured to open up the "dumbbell" shape to a fully opened circle shaped product (see col. 4, ll. 13-15). Abarzua et al. fails to disclose decoupling an amplification target circles associated with the analytes from the specific binding molecules.

Claims 1-11, 23-24- 27-65, 70-102, 107-136 are directed to methods of detecting one or more analytes. The claims require the use of specific binding molecules and amplification target circles. As claimed, the reporter binding molecules comprise a specific binding molecule and an

amplification target circle. That is, the claimed reporter binding molecules include as a component an amplification target circle. After the specific binding molecule portion of the reporter binding molecule interacts with its cognate analyte, the amplification target circle that is part of that reporter binding molecule is decoupled from the specific binding molecule. The decoupled amplification target circle is then replicated. Thus, the claims require at least (1) a reporter binding molecule that includes both a specific binding molecule (that can interact with an analyte) and an amplification target circle, (2) decoupling of that amplification target circle associated with the analyte from that specific binding molecule, and (3) replication of the decoupled amplification target circle.

The Office Action alleges on page 6, lines 7-14, that Abarzua et al. teaches a method that comprises decoupling of amplification target circles facilitated by heat denaturation (raising the temperature to disrupt base-pairing). The Office Action relies on col. 3, lines 48-67 and col. 4, lines 1-15 and 51-67 of Abarzua et al. in support of its allegation. However, the cited passage is actually drawn to the use of heat to disrupt the dumbell structure of a single-stranded DNA molecule in order to allow the dumbbell structure to open into a circular structure to be used in rolling circle replication. There is only a single molecule involved, therefore, there is no release of one molecule from another and certainly no disclosure of decoupling an amplification target circle from a reporter binding molecule. In fact, there is no indication or disclosure of a reporter binding molecule, much less a relationship between a reporter binding molecule and an amplification target circle wherein the amplification target circle associated with the anaylte is dissociated from a specific binding molecule in the portions of Abarzua et al. cited by the Office Action.

Thus, neither Lizardi et al. nor Abarzua et al. disclose or suggest decoupling of amplification target circles associated with an analyte from their associated specific binding molecules prior to replication of the amplification target circles. Lizardi et al. and Abarzua et al., either alone or in combination, fail to disclose or suggest every feature of the claims. Accordingly, for at least these reasons, Lizardi et al. and Abarzua et al. fail to make obvious claims 1-11, 23-24- 27-65, 70-102, 107-136.

B. Claims 1-136 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kingsmore et al. (U.S. Pat. No. 6,531,283) in view of Abarzua (U.S. Pat. No. 6,498,023). Applicants respectfully traverse this rejection to the extent it applies to the claims as amended.

Applicants note that the rejection applies Abarzua et al. in the same way and for the same disclosure for which Abarzua et al. was applied in the rejection of claims 1-11, 23-24- 27-65, 70-102, 107-136 under 35 U.S.C. § 103(a). For at least the reasons discussed above in connection with the rejection of claims 1-11, 23-24- 27-65, 70-102, 107-136 under 35 U.S.C. § 103(a), Abarzua et al. fails to disclose or suggest every limitation of claims 1-136. Specifically. Abarzua et al. fails to disclose or suggest decoupling of an amplification target circle associated with an analyte from a specific binding molecule.

Kingsmore et al., which was cited for its teaching of a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte, fails to supplement the missing elements from Abarzua et al. In fact, the Office Action admits that Kingsmore et al. fails to teach decoupling of amplification target circles associated with an analyte from the pecific binding molecules.

Thus, neither Kingsmore et al. nor Abarzua et al. disclose or suggest decoupling of amplification target circles associated with an analyte from their associated specific binding molecules prior to replication of the amplification target circles. Kingsmore et al. and Abarzua et al., either alone or in combination, fail to disclose or suggest every feature of the claims. Accordingly, for at least these reasons, Kingsmore et al. and Abarzua et al. fail to make obvious claims 1-136.

Double Patenting Rejection

Claims 1-136 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,531,283 to Kingsmore et al. in view of U.S. Pat. No. 6,498,023 to Abarzua et al. Applicants respectfully traverse this rejection to the extent it applies to the claims as amended.

Applicants first direct the Examiner to the currently amended claims that now recite, in part, "decoupling the amplification target circles associated with the analytes from the specific

binding molecules,". These amendments were made in response to the Examiner's comments that such amendments clarified the claims. Applicants further submit that Abarzua et al. does not disclose what is alleged in the Office Action and, as a result, the combination of the claims of Kingsmore et al. and Abarzua et al. do not disclose or suggest what is presently claimed. In addition, there is no teaching, motivation or suggestion to combine the claims of Kingsmore et al. and the teachings of Abarzua et al. to achieve the subject matter of the current claims. These errors render the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness.

Applicants submit that, even considered together, Abarzua et al. and the claims of Kingsmore et al. fail to disclose and suggest every feature of the claimed method. Applicants also submit that statements in the Office Action to the effect that Abarzua et al. teaches decoupling of amplification target circles associated with anayltes from specific binding molecules are incorrect. Abarzua et al. included no such disclosure and cannot be interpreted as making such a disclosure, and the Office Action fails to address these points.

The claims of Kingsmore et al. are drawn to a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. The claims of Kingsmore et al. fails to disclose decoupling of the amplification target circle associated with the analyte from the specific binding molecule. In fact, the Office Action admits that Kingsmore et al. fails to disclose a decoupling step to dissociate an amplification target circle from a reporter binding molecule.

Abarzua et al. discloses a method of synthesizing single-stranded DNA circles of varying size and sequence that are capable of ready use in subsequent processes, such as rolling circle replication (see col. 3, lines 35-47). The method employs the use of hairpin oligonucleotides, each circularized by internal complementary sequences, which are then permitted to anneal to each other via complementary overhangs or coherent tail sequences. After the hairpin

oligonucleotides have annealed to one another, the ends of the hairpin oligonucleotides are ligated together to provide a larger single-stranded DNA circle in the form of what Abarzua et al. terms a "dumbbell" (see col. 3, line 67 – col. 4, line 10). Following ligation, the "dumbbell" shaped DNA circle is heat denatured to open up the "dumbbell" shape to a fully opened circle shaped product (see col. 4, ll. 13-15). Abarzua et al. fails to disclose decoupling of an amplification target circle associated with the analyte from a specific binding primer.

Claims 1-11, 23-24- 27-65, 70-102, 107-136 are directed to methods of detecting one or more analytes. The claims require the use of specific binding molecules and amplification target circles. As claimed, the reporter binding molecules comprise a specific binding molecule and an amplification target circle. That is, the claimed reporter binding molecules include as a component an amplification target circle. After the specific binding molecule portion of the reporter binding molecule interacts with its cognate analyte, the amplification target circle that is part of that reporter binding molecule is decoupled from the reporter binding molecule. The decoupled amplification target circle is then replicated. Thus, the claims require at least (1) a reporter binding molecule that includes both a specific binding molecule (that can interact with an analyte) and an amplification target circle, (2) decoupling of that amplification target circle associated with the analyte from that specific binding molecule, and (3) replication of the decoupled amplification target circle.

The Office Action alleges on page 15, lines 3-10 that Abarzua et al. teaches a method that comprises decoupling of amplification target circles from themselves facilitated by heat denaturation (raising the temperature to disrupt base-pairing). The Office Action relies on col. 3, lines 48-67 and col. 4, lines 1-15 and 51-67 of Abarzua et al. in support of its allegation. However, the cited passage is actually drawn to the use of heat to disrupt the dumbell structure of a single-stranded DNA molecule in order to allow the dumbbell structure to open into a circular structure to be used in rolling circle replication. There is only a single molecule involved, therefore, there is no release of one molecule from another and certainly no disclosure of decoupling an amplification target circle associated with the analyte from the specific binding molecule. In fact, there is no indication or disclosure of a speicific binding molecule, much less a relationship between a specific binding molecule and an amplification target circle wherein the

amplification target circle associated with an analyte is dissociated from a specific binding molecule in the portions of Abarzua et al. cited by the Office Action.

Thus, neither Abarzua et al. nor the claims of Kingsmore et al. disclose or suggest decoupling of amplification target circles associated with an analyte from their associated specific binding molecules prior to replication of the amplification target circles. The claims of Kingsmore et al. and Abarzua et al., either alone or in combination, fail to disclose or suggest every feature of the claims. Accordingly, for at least these reasons, the claims of Kingsmore et al. and Abarzua et al. fail to make obvious claims 1-136.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $455.00, representing $60.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(1) and $395.00 for the fee for a small entity under 1.17(e), as well as a Request For Extension of Time and a Request for Continued Examination are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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